Establishing a New Path Forward for Patients With Severe Symptomatic Aortic Stenosis

THE PARTNER TRIAL
CLINICAL RESULTS

EDWARDS TRANSCATHETER HEART VALVE PROGRAM
Definitive Results Through Rigorous Design

Survival rates after the onset of symptoms in severe aortic stenosis are dismal, as low as 50% at 2 years and 20% at 5 years.\textsuperscript{1} Surgical aortic valve replacement (AVR) is the current standard of care, but it has been estimated that between 30% and 60% of patients do not undergo AVR.\textsuperscript{2,3}

The PARTNER Trial (Placement of AoRtic TraNscathetER Valves) was initiated to investigate the safety and effectiveness of a less invasive treatment in this population. The world’s first prospective, randomized, and controlled trial for transcatheter aortic valve implantation (TAVI),\textsuperscript{4} The PARTNER Trial sets the standard in site selection, case screening, study management, multidisciplinary teamwork, and patient follow-up. Methodology required top-performing surgical capability in order to set the highest possible standard for comparison to TAVI.

The PARTNER Trial consists of two individually powered patient cohorts.

- In Cohort A, the safety and effectiveness of the balloon-expandable Edwards SAPIEN Transcatheter Heart Valve (THV) was compared to AVR in high-risk patients with severe symptomatic aortic stenosis.\textsuperscript{4}

- In Cohort B, the safety and effectiveness of the balloon-expandable Edwards SAPIEN THV was compared to standard therapy (best medical management) in inoperable patients with severe symptomatic aortic stenosis.\textsuperscript{5}
**THE PARTNER TRIAL PROTOCOL**

**ASSESSMENT**

- **Operability**
  - Yes
  - No

**2 Cohorts**

- **Cohort A**
  - n = 699
  - Individually Powered
  - (N = 1,057)
  - Transfemoral Access
    - Yes
    - No
    - TF (n = 492)
    - TA (n = 207)

- **Cohort B**
  - n = 358
  - Transfemoral Access
    - Yes
    - No
    - TF (n = 244)
    - TA (n = 104)

**1:1 Randomization**

- TF TAVI (n = 244) vs. AVR (Control) (n = 248)
- TA TAVI (n = 104) vs. AVR (Control) (n = 103)
- TF TAVI (n = 179) vs. Standard Therapy (Control) (n = 179)

**COHORT A INCLUSION CRITERIA**

- STS score ≥ 10
- Predicted operative mortality ≥ 15%
- NYHA functional class ≥ II
- AVA < 0.8 cm²
- Mean AVG > 40 mm Hg
- Peak jet velocity > 4.0 m/s

**COHORT B INCLUSION CRITERIA**

- STS score 11.6
- Predicted operative mortality > 50%
- NYHA functional class ≥ II
- AVA < 0.8 cm²
- Mean AVG > 40 mm Hg
- Peak jet velocity > 4.0 m/s

*This mean score reflects enrolled patient group; not required for inclusion.

†Patient selection required at least two cardiothoracic surgeons and an interventional cardiologist to agree that patients were not suitable candidates for surgery.4,5

AVA, aortic valve area; AVG, aortic valve gradient; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; TA, transapical; TF, transfemoral.
Survival With Edwards SAPIEN THV Was Equivalent to AVR in High-Risk Patients

Primary endpoint: All-cause mortality at 1 year (ITT)4

Mortality at 1 year

Edwards SAPIEN THV 24.2%
AVR 26.8%

(P = .001 for non-inferiority)4

Results for both procedures exceeded expectations*4,6

AVR
Expected 30-day mortality rate: 11.8%
Observed 30-day mortality rate: 8.0%
O:E ratio = 0.68

Edwards SAPIEN THV
Expected 30-day mortality rate: 11.7%
Observed 30-day mortality rate: 5.2%
O:E ratio = 0.44

*As-treated (AT) analysis.
ITT, intent to treat.
Transfemoral Approach Equivalent to AVR

Transfemoral TAVI subgroup non-inferior to AVR ($P = .002$)$^4$

Transapical Approach Results

While not powered for independent statistical analysis, the transapical TAVI subgroup showed similar results as AVR at 1 year$^4$
Clinical Outcomes: High-Risk Patients

Both TAVI and AVR were associated with important but different periprocedural hazards.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>30 Days&lt;sup&gt;4&lt;/sup&gt;</th>
<th>1 Year&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edwards SAPIEN THV (n = 348)</td>
<td>AVR (n = 351)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>3.4%</td>
<td>6.5%</td>
</tr>
<tr>
<td>All Stroke or TIA</td>
<td>5.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>3.8%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Major Vascular Complications</td>
<td>11.0%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>9.3%</td>
<td>19.5%</td>
</tr>
<tr>
<td>New Atrial Fibrillation</td>
<td>8.6%</td>
<td>16.0%</td>
</tr>
<tr>
<td>New Pacemaker</td>
<td>3.8%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack.

Edwards SAPIEN THV: Statistically higher incidence of all stroke or TIA and major vascular complications<sup>4</sup>

AVR: Statistically higher incidence of major bleeding and new atrial fibrillation<sup>4</sup>
EDWARDS SAPIEN THV IMPROVED
Hemodynamics and Sustained Valve Performance

**ECHO FINDINGS: AORTIC VALVE GRADIENTS**

![Graph showing hemodynamics](graph.png)

- **Mean and Peak Gradient**
- **As-Treated Trial Arms**
- **(mm Hg)**
  - **Peak Gradient – AVR**
  - **Peak Gradient – TAVI**
  - **Mean Gradient – AVR**
  - **Mean Gradient – TAVI**

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<thead>
<tr>
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<th>Edwards THV</th>
<th>AVR</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>n = 327</td>
<td>n = 301</td>
</tr>
<tr>
<td>30 Days</td>
<td>n = 287</td>
<td>n = 231</td>
</tr>
<tr>
<td>1 Year</td>
<td>n = 227</td>
<td>n = 159</td>
</tr>
</tbody>
</table>

**Edwards SAPIEN THV Rapidly Improved Symptoms, With Results Equivalent to AVR at 1 Year**

**NYHA FUNCTIONAL CLASS**

![Bar chart showing NYHA class I to IV](chart.png)

- **P = 1.00**
- **P < .001**
- **P = .75**

- **85%** of patients in NYHA class I or II at 1 year

- **Symptom improvement favored Edwards SAPIEN THV at 30 days and was similar to that with AVR at 1 year**

*A range of surgical valve sizes were used in the AVR arm and both the 23 mm and the 26 mm SAPIEN valves were used in the TAVI arm. Edwards surgical valves were used in 90% of patients in the AVR arm.*

**ESTABLISHING A NEW PATH FORWARD FOR PATIENTS WITH SEVERE SYMPTOMATIC AORTIC STENOSIS**
Edwards SAPIEN THV Significantly Improved Survival in Inoperable Patients

COHORT B

THE PARTNER TRIAL

Edwards SAPIEN THV Significantly Improved Survival in Inoperable Patients

Co-primary endpoint: All-cause mortality

20% absolute reduction in mortality

Despite expert care and frequent BAV (78.2%), standard therapy failed to alter the dismal natural course of disease

24% absolute reduction in cardiovascular mortality at 1 year \((P < .001)\)

29% absolute reduction in all-cause mortality or repeat hospitalization at 1 year (co-primary endpoint; \(P < .001\))

NNT = 5

Need to treat just 5 patients with an Edwards SAPIEN THV to save a life
Edwards SAPIEN THV Significantly Improved Symptoms and Quality of Life*

- Significant improvement observed as early as 30 days ($P < .001$)\textsuperscript{5}
- 25-point treatment effect in KCCQ score\textsuperscript{6}
- 20-point improvement in KCCQ score represents change of large clinical importance\textsuperscript{7}

\textsuperscript{*}NYHA and KCCQ scores of surviving patients only.

BAV, balloon aortic valvuloplasty; KCCQ, Kansas City Cardiomyopathy Questionnaire; MCID, minimum clinically important difference.
The PARTNER Trial: Critical Insights

Extraordinary news for patients
Both TAVI with Edwards SAPIEN THV—delivered transfemorally and transapically—and AVR offer meaningful, life-changing benefits for patients with severe symptomatic aortic stenosis who are in critical need.

TAVI with Edwards SAPIEN THV is the new standard of care for patients with inoperable severe symptomatic aortic stenosis

NNT = 5
Need to treat just 5 patients to save a life

Both treatments have considerations
TAVI and AVR were associated with important but different periprocedural hazards that merit consideration by clinicians.

<table>
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<th>Edwards SAPIEN THV</th>
<th>Surgical AVR</th>
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<td>Statistically higher incidence of all stroke and TIA and major vascular complications</td>
<td>Statistically higher incidence of major bleeding and new atrial fibrillation</td>
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It takes a team
The multidisciplinary heart team—with interventional cardiologists and cardiothoracic surgeons leading the way—leverages The PARTNER Trial approach for remarkable patient outcomes.
The PARTNER Trial: Investigator Interpretations

“On the basis of a rate of death from any cause at 1 year that was 20 percentage points lower with TAVI than with standard therapy, balloon-expandable TAVI should be the new standard of care for patients with aortic stenosis who are not suitable candidates for surgery.”


“This is the ideal opportunity, because surgical AVR is one of the most effective operations surgeons offer, and TAVR is the most exciting new treatment for aortic stenosis in the past two to three decades. This opens up a new set of patients who may very well benefit as much by TAVR as by the conventional gold standard surgery.”

— Craig R. Smith, MD, Chief, Division of Cardiothoracic Surgery, New York-Presbyterian Hospital, Columbia University Medical Center, New York, and the Co-principal Investigator of The PARTNER Trial

“These extraordinary results are accomplished because of an unprecedented teamwork between a cardiologist, cardiac surgeon, and the associated caregivers.”

— E. Murat Tuzcu, MD, Vice Chairman, Department of Cardiology in the Sydell and Arnold Heart & Vascular Institute, Cleveland Clinic, and Investigator, The PARTNER Trial

TAVR, transcatheter aortic valve replacement.
Both TAVI, delivered transfemorally or transapically, and AVR showed reduced mortality, improved hemodynamics, and improvement of symptoms in high-risk patients

— Outcomes were better than expected for all three treatment groups

TAVI reduced mortality, improved hemodynamics, and remarkably improved symptoms in inoperable patients